REMARKS

Previously, claims 64-77 were pending. In the present amendment, claims 64, 68 and 70 are amended, and claims 71 and 72 are canceled. Applicants reserve the right to pursue the canceled subject matter in one or more related patent applications.

Claims 64, 68, 70 and 73 have been amended for purposes of clarity. In particular, claim 64 has been amended to delete the phrase "or are identical to each other within the complementarity determining regions (CDRs) and have at least 95% sequence identity to each other outside of the CDRs." Claim 70 has been amended to incorporate the limitations of claims 71 and 72.

No new matter is added by these amendments. Upon entry of this Amendment, claims 64-70 and 73-77 will be pending in the present application.

I. Rejections for Obviousness-Type Double Patenting

The Examiner provisionally rejects claims 64-77 on the ground of non-statutory obviousness-type double patenting over claims 56-77 of co-pending Application No. 09/373,403 (Office Action at page 4). The Examiner also rejects claims 64-77 on the ground of non-statutory obviousness-type double patenting over claims 45-82 of U.S. Patent No. 7,183,076. Applicants respectfully request that any rejections on the ground of non-statutory obviousness type double patenting over claims of Application No. 09/373,403 and U.S. Patent No. 7,183,076 be held in abeyance until allowable subject matter is indicated, at which time Applicants will take appropriate action.

II. The Rejection Under 35 U.S.C. § 112, 1st Paragraph

The Examiner rejects claims 64-77 under 35 U.S.C. § 112, 1st paragraph as allegedly failing to comply with the written description requirement. In particular, the Examiner contends that it does not appear that Applicants were in possession of a multispecific antibody comprising useful light chains that differ in their amino acid sequence outside the CDR regions, and that the specification fails to provide explicit support for bispecific antibodies having common light chains, wherein the common light chains are not identical in amino acid sequence to each other. Office Action at pages 4-5.

Without conceding the propriety of the Examiner's contentions, Applicants point out that independent claim 64 has been amended to delete the phrase "or are identical to each other within the complementarity determining regions (CDRs) and have at least 95%

sequence identity to each other outside of the CDRs." Accordingly, Applicants believe that the rejection under 35 U.S.C. § 112, 1st paragraph is obviated, and respectfully request withdrawal of the rejection.

III. The Rejection Under 35 U.S.C. § 102(b)

The Examiner rejects claims 64, 65, 69, 70, 72 and 76 as allegedly being anticipated by Tachibana *et al.*, *Hum. Antibod. Hybridomas* 4:42-46 (1993) (hereinafter "Tachibana"). The Examiner contends that Tachibana teaches a bispecific antibody comprising two different heavy chains and one light chain. Office Action at pages 5-6. Applicants respectfully traverse the rejection as follows.

The legal standard for anticipation under 35 U.S.C. § 102(b) is one of strict identity. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co.*, 814 F. 2d 628, 631, 2 U.S.P.Q.2d 1051, 1052-53 (Fed. Cir. 1987). An anticipating reference must describe and enable the claimed invention, including all the claim limitations, with sufficient clarity and detail to establish that the subject matter already existed in the prior art and that its existence was recognized by persons of ordinary skill in the field of the invention. *In re Spada*, 911 F.2d 705 (Fed. Cir. 1990); *Crown Operations International, Ltd. V. Solutia Inc.*, 289 F.3d 1367, 1375 (Fed. Cir. 2002).

Moreover, a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is *necessarily present*, or inherent in the single anticipating reference. *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) (quoting *Continental Can Co. v. Monsanto Co.*, 948, F.2d 1264, 1268, (Fed. Cir. 1991) (internal quotations omitted; emphasis supplied). The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (emphasis supplied). "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original).

Applicants respectfully submit that Tachibana does not expressly nor inherently teach all the elements of instant claims. Independent claim 64 recites a multispecific antibody

comprising four polypeptides, wherein a first and a second of said polypeptides each comprise a heavy chain constant domain and a heavy chain variable domain, and a third and a fourth of said polypeptides are each common light chains that are identical to each other, wherein said first polypeptide and said third polypeptide form a binding domain that binds a first antigen, and wherein said second polypeptide and said fourth polypeptide form a binding domain that binds a different antigen, and **wherein said first polypeptide and said second polypeptide dimerize to form a multispecific antibody**. Furthermore, independent claim 70 recites a multispecific antibody comprising two heteromeric polypeptides and two light chains wherein the first heteromeric polypeptide comprises a first heavy chain variable domain and a first multimerization domain; the second heteromeric polypeptide comprises a second heavy chain variable domain and a second multimerization domain; wherein the two light chains have an amino acid sequence identity of 100%, **wherein the first and second heteromeric polypeptides dimerize by interaction of the first and second multimerization domains to form a multispecific antibody**.

Tachibana discloses a hybrid hybridoma, clone A9C11, which produces a bifunctional antibody having dual specificity for porcine carboxypeptidase A (Cpase) and double-stranded (ds DNA), wherein the light chains of the antibody consist of only the light chains derived from the parental anti-ds DNA antibody (*see* abstract). While Tachibana discloses at page 45 (text bridging left and right columns) that the bifunctional antibody produced by A9C11 comprises the heterologous association of heavy and light chains, *e.g.*, that the μ heavy chain derived from the anti-Cpase antibody (6T-C5) is associated with the λ light chain derived from the anti-ds DNA antibody (5B-SU), Tachibana does not expressly disclose the heterologous association of a first heavy chain polypeptide and a second heavy chain polypeptide, which first and second heavy chain polypeptides each combine with a common light chain to bind two different antigens, as recited in the instant claims. In other words, Tachibana does not expressly disclose that the μ heavy chain derived from the anti-Cpase antibody (6T-C5) is associated with the μ heavy chain derived from the anti-ds DNA antibody (5B-SU), much less that these two different heavy chains dimerize and are further associated with the same light chain. Accordingly, Tachibana does not *expressly* anticipate any of the instant claims.

Applicants further submit that Tachibana does not anticipate the instant claims under a legal standard of *inherent* anticipation. Tachibana discloses that the bifunctional antibodies

produced by clone A9C11 are IgM-class monoclonal antibodies. Applicants submit herewith as Exhibit A excerpts from the textbook *Antibodies: A Laboratory Manual* (1988), pages 10-11, Table 2.1, which indicate that an IgM molecule contains five Y-shaped units arranged in a pentameric array, with each Y-unit containing two heavy chains and two light chains which make up two antigen binding sites, with each IgM molecule having a total of ten antigen binding sites. *See, e.g.,* Exhibit A, page 10. Thus, the bifunctionality of the IgM-class antibody disclosed by Tachibana could readily arise from at least two Y-units being specific for a different antigen within the same IgM molecule; however, any single Y-unit within the IgM molecule would comprise two identical heavy chain polypeptides in association with one another. Indeed, Tachibana acknowledges that such an "autologous heavy-heavy chain combination occurred preferentially in hybrid hydridomas." *See* Tachibana at page 45, right column.

Applicants respectfully submit that nothing in Tachibana indicates that the bifunctionality of the IgM-class antibody is a result of the two antigen binding sites within the *same* Y-unit having specificity for two different antigens, wherein the two antigen binding sites are formed from two different heavy chain polypeptides and an identical light chain, as required by the instant claims. Even assuming *arguendo* that such a bifunctional antibody *may* be formed by A9C11, this mere possibility would not be sufficient for Tachibana to anticipate the instant claims, since there has been no showing by the PTO that such an antibody is *necessarily* produced by A9C11. (The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531; "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461).

Because Tachibana neither expressly or inherently discloses a multispecific antibody comprising two different heavy chain polypeptides which associate with a common light chain to form two different antigen binding sites, and which dimerize with one another to form the multispecific antibody, Tachibana does not expressly or inherently anticipate any of claims 64-70 and 73-77 under 35 U.S.C. § 102(b). Applicants thus respectfully request withdrawal of the rejection.

CONCLUSION

Applicants believe that the claims of the instant amendment meet all of the conditions for patentability and are in condition for allowance. Accordingly, an indication of the same is respectfully requested. If any issues remain in connection with this application, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

No fees are believed to be due in connection herewith other than the Information Disclosure Statement fee. However, should the Commissioner determine otherwise, please charge the required fee to Jones Day Deposit Account No. 50-3013 (referencing 403545-999481).

Respectfully submitted,

Date: June 30, 2010

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EXHIBIT A:

***Antibodies: A Laboratory Manual* (1988), Pages 10-11, Table 2.1**

Antibodies

A LABORATORY MANUAL

Ed Harlow
Cold Spring Harbor Laboratory

David Lane
Imperial Cancer Research Fund Laboratories

Cold Spring Harbor Laboratory
1988

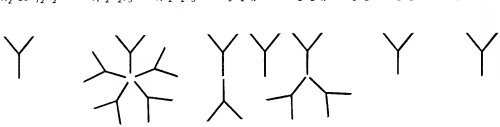
heavy chains fold together to make the Fc domain. The four polypeptide chains are held together by disulfide bridges and noncovalent bonds.

In addition to the IgG molecules, serum contains other classes of antibody molecules

The other antibody classes, IgM, IgA, IgE, and IgD, are distinguished by the type of heavy chain found in the molecule. Where IgG molecules have heavy chains known as γ-chains, IgMs have μ-chains, IgAs have α-chains, IgEs have ϵ-chains, and IgDs have δ-chains. The differences in the heavy-chain polypeptides allow these proteins to function in different types of immune responses and at particular stages of the maturation of the immune response. The protein sequences responsible for these differences are found primarily in the Fc fragment. Different classes of antibodies may also vary in the number of Y-like units that join to form the complete protein. IgM antibodies, for example, have five Y-shaped units. Because each Y unit has two antigen binding sites, IgMs have 10 identical antigen binding sites. The sites for association between the different Y units are also found in the Fc region. Table 2.1 summarizes many of the properties of these antibody classes.

While there are five different types of heavy chains, there are only two light chains, κ and λ. One light chain always associates with one

TABLE 2.1
Classes of Antibodies

Characteristics	IgG	IgM	IgA	IgE	IgD
Heavy Chain	γ	μ	α	ε	δ
Light Chain	κ or λ	κ or λ	κ or λ	κ or λ	κ or λ
Molecular Formula	$\gamma_2\kappa_2$ or $\gamma_2\lambda_2$	$(\mu_2\kappa_2)_5$ or $(\mu_2\lambda_2)_5$	$(\alpha_2\kappa_2)_n$ [a] or $(\alpha_2\lambda_2)_n$	$\varepsilon_2\kappa_2$ or $\varepsilon_2\lambda_2$	$\delta_2\kappa_2$ or $\delta_2\lambda_2$
Y Structure					
Valency	2	10	2, 4, or 6	2	2
Concentration in Serum	8–16 mg/ml	0.5–2 mg/ml	1–4 mg/ml	10–400 ng/ml	0–0.4 mg/ml
Function	Secondary response	Primary response	Protects mucous membranes	Protects against parasites (?)	?

[a] $n = 1$, 2, or 3.

heavy chain, so the total number of light chains will always equal the number of heavy chains. Since the basic structural Y unit has two heavy chains and two light chains, IgMs, which have five Y-units, have 10 light chains and 10 heavy chains. However, any one antibody molecule will have only one type of light chain and one type of heavy chain. There are no restrictions on which types of heavy or light chains can form antibodies, so antibodies of all classes (i.e., with different heavy chains) can contain either κ or λ light chains.

Comparison of the primary amino acid sequences of light chains reveals a constant and a variable region

Light chains are approximately 220 amino acids long and can be divided into two regions, each about 110 amino acids in length (Fig. 2.5). When sequences from a number of light chains were first com-

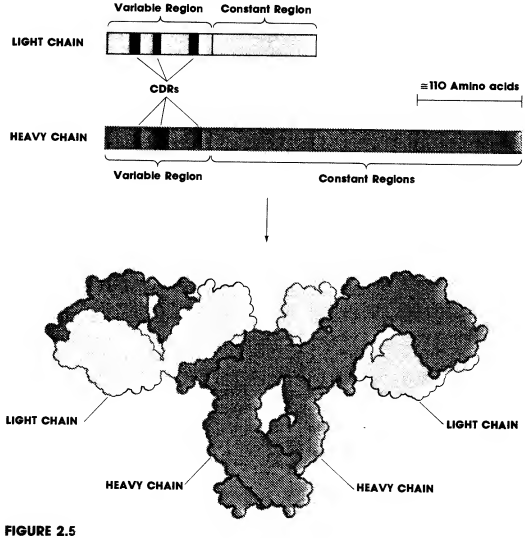


FIGURE 2.5
Light- and heavy-chain structure. (Adapted from Silverton et al. 1977.)